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Telithromycin in the treatment of pneumococcal community-acquired respiratory tract infections: a review

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Summary

Objectives: A pooled analysis of 14 Phase III studies was performed to establish the clinical and bacteriologic efficacy of telithromycin 800 mg once daily in the treatment of pneumococcal community-acquired respiratory tract infections (RTIs).
Methods: Data were examined from 5534 adult/adolescent patients with community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB), or acute bacterial sinusitis, who had received telithromycin for 5—10 days or a comparator antibacterial.
Results: Streptococcus pneumoniae was identified in 704/2060 (34.2%) bacteriologically evaluable patients. The respective per-protocol clinical cure rates for telithromycin and comparators were 94.3% and 90.0% (CAP); 81.5% and 78.9% (AECB); 90.1% and 87.5% (acute sinusitis); 92.7% and 87.6% (all indications). Clinical cure rates were 28/34 (82.4%) and 5/7, respectively, for penicillin-resistant infections, and 44/52 (84.6%) and 11/14, respectively, for erythromycin-resistant infections. Of 82 patients with pneumococcal bacteremia, 74 (90.2%) were clinically cured after telithromycin treatment, including 5/7 and 8/10 with penicillin- or erythromycin-resistant strains, respectively. Adverse events considered possibly related to study medication were reported by 1071/4045 (26.5%) telithromycin and 505/1715 (29.4%)

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comparator recipients. These events were generally of mild/moderate severity, and mainly gastrointestinal in nature.
Conclusions: As *S. pneumoniae* is the leading bacterial cause of community-acquired RTIs, and antibacterial resistance is increasing among this species, these findings support the use of telithromycin as first-line therapy in this setting.

Introduction

Community-acquired respiratory tract infections (RTIs) such as community-acquired pneumonia (CAP), acute bacterial exacerbations of chronic bronchitis (AECB), and acute sinusitis are among the most common diseases in industrialized countries, and are associated with a massive consumption of healthcare resources.[1] The total annual cost of treatment of CAP is US$8.4 billion in the USA alone,[2] and CAP is responsible for approximately 4.5 million visits to physicians' offices, emergency departments, and outpatient clinics annually. In comparison, the total annual treatment cost for AECB in the USA is approximately US$1.6 billion.[3] For both these diseases, more than three-quarters of the annual treatment cost is accounted for by inpatient care. An estimate for 1996 indicated that the overall direct healthcare expenditure attributable to sinusitis in the USA was US$5.8 billion.[4]

In addition to this appreciable socioeconomic burden, community-acquired RTIs are associated with considerable morbidity, and can be fatal in vulnerable individuals if left untreated.[5–9] Despite the high prevalence of viral disease, a substantial proportion of RTIs are still bacterial.[6,8,10,11] These infections require prompt attention with effective therapies to shorten the duration of symptoms, prevent progression to severe disease, eradicate the causative pathogen(s), and — importantly — prevent serious and sometimes life-threatening complications such as bacteremia, meningitis, and sepsis.

Streptococcus pneumoniae is the most common causative bacterial pathogen identified in community-acquired RTIs, accounting for 20–60% of CAP cases[12] (including around two-thirds of all cases of bacteremic pneumonia[6]), 15–22% of AECB cases,[10] and up to 54% of acute bacterial sinusitis cases.[11,13] Patients with these infections are typically treated empirically, so it is important that first-line therapies can be relied upon to eradicate *S. pneumoniae* as well as the other common pathogens seen in this setting (*Haemophilus influenzae*, *Moraxella catarrhalis*, and atypical/intracellular organisms such as *Chlamydophila* [*Chlamydia*] *pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella* spp.). Recent surveillance studies have documented alarming rises in global pneumococcal resistance to a variety of antibacterials in common use, including current first-line β-lactams and macrolides.[14,15] Although there is little clinical evidence to suggest that these agents should not still be used to treat RTIs, agents with a spectrum of activity covering resistant strains may be expected not only to minimize the risk of poor clinical outcome and potentially fatal purulent complications, but also to lessen any potential contribution to the growing resistance that may limit empiric treatment options.

Telithromycin is the first of a new class of antibacterials — the ketolides — to be approved for clinical use in the first-line treatment of community-acquired RTIs. This agent has a spectrum of activity that specifically targets common bacterial respiratory pathogens (*S. pneumoniae* [including isolates resistant to erythromycin and/or penicillin], *Streptococcus pyogenes*, *H. influenzae* and *M. catarrhalis*,[16,17] and atypical/intracellular organisms[18,19]). The efficacy and safety of telithromycin 800 mg once daily in patients with community-acquired RTIs have been studied in 16 Phase III clinical trials[20–35], many of which compared the drug with one of a number of antibacterials regarded as representative of current standards of care. These included cefuroxime axetil, high-dose amoxicillin or amoxicillin–clavulanate, penicillin V (for tonsillopharyngitis), and new-generation macrolides and quinolones. This paper presents a pooled analysis of 14 of these studies (excluding tonsillopharyngitis studies as no patients had pneumococcal infection), which specifically assessed the clinical and bacteriologic efficacy of telithromycin in community-acquired RTIs caused by *S. pneumoniae* — the most common and potentially serious bacterial cause of such infections.

Methods

Patients and bacteriologic methods

The 14 Phase III studies involved a total of 5534 adult (>18 years) or adolescent (13–18 years) patients who had been treated for CAP (mild to moderate

severity), AECB, or acute bacterial sinusitis (Table 1). Patients received either oral telithromycin 800 mg (2 × 400 mg capsules) once daily (n = 881) for 5—10 days (depending on the condition being treated) or a comparator antibacterial agent (n = 1653) that was first-line at the time of the study (see Table 1 for details of individual drugs and regimens). The nine studies that included a comparator arm were of a randomized, double-blind design, with all comparator drugs given as 10- or 7- to 10-day courses (Table 1). All studies were carried out in accordance with the provisions of the latest revisions of the Declaration of Helsinki and were in compliance with Good Clinical Practice regulations. Protocols were approved by the relevant ethics committees at each institution, and written informed consent was obtained from all participants before enrollment.

Pathogens were isolated from blood, respiratory secretion, or sinus aspirate cultures. The respiratory pathogens isolated from these samples and considered by the examining investigator to be responsible for infection were defined as causative organisms. Strains of *S. pneumoniae* isolated from sample cultures were tested for their susceptibility to penicillin, erythromycin, and telithromycin by determination of minimum inhibitory concentrations (MICs) and disk zone inhibition at a central reference laboratory using National Committee for Clinical Laboratory Standards (NCCLS) recommended criteria and methodology.[36,37] Intermediate susceptibility to penicillin was defined as an MIC

Table 1 Summary of 14 clinical trials of telithromycin 800 mg once daily in patients with pneumococcal community-acquired respiratory tract infections.

Study No.	Telithromycin		Comparator		
	No. of patients		Regimen	No. of patients	
	All (mITT/bmITT)	*S. pneumoniae* (bmITT)[a]		All (mITT/bmITT)	*S. pneumoniae* (bmITT)[a]
Community-acquired pneumonia					
3001 (10 days)[22]	199/62	32	AMX 1 g tid (10 days)	205/63	34
3006 (10 days)[34]	204/48	25	CLA 500 mg bid (10 days)	212/45	23
3009 (7—10 days)[31]	100/32	11	TVA 200 mg daily (7—10 days)	104/34	9
4003 (5 or 7 days)[25]	378/234	77	CLA 500 mg bid (10 days)	181/102	38
3000 + 3009OL (7—10 days)[26,28]	452/165	82	—	—	—
3010 (7 days)[20]	418/255	76	—	—	—
3012 (7 days)[35]	538/265	110	—	—	—
Acute exacerbations of chronic bronchitis					
3003 (5 days)[21]	160/50	12	AMC 500/125 mg tid (10 days)	160/44	8
3007 (5 days)[33]	182/32	3	CXM 500 mg bid (10 days)	191/35	7
3013 (5 days)[29]	270/90	14	CLA 500 mg bid (10 days)	282/88	9
Acute sinusitis					
3002 (5 or 10 days)[24]	335/201	70	—	—	—
3005 (5 or 10 days)[30]	405/18	6	AMC 500/125 mg tid (10 days)	202/11	5
3011 (5 days)[27]	240/126	37	CXM 250 mg bid (10 days)	116/60	16
Totals	3881/1578	555		1653/482	149

AMC, amoxicillin—clavulanate; AMX, amoxicillin; bid, twice daily; bmITT, bacteriologically evaluable modified intent to treat population; CLA, clarithromycin; CXM, cefuroxime axetil; mITT, modified intent to treat population; tid, three-times daily; TVA, trovafloxacin.

[a] As either the sole pathogen or in combination with another pathogen(s).

of 0.12—1.0 mg/L; strains with MICs $\geq$ 2.0 mg/L were considered resistant and those with MICs $\leq$ 0.06 mg/L were considered susceptible. Resistance to erythromycin was defined as an MIC of $\geq$1.0 mg/L; susceptibility was defined as an MIC $\leq$ 0.25 mg/L. Susceptibility to telithromycin was defined using tentative NCCLS breakpoints (as approved by the Subcommittee on Antimicrobial Testing, January 2003): MIC $\leq$ 1.0 mg/L (susceptible); MIC 2.0 mg/L (intermediate); and MIC $\geq$ 4.0 mg/L (resistant).

Clinical and bacteriologic outcomes

Clinical and bacteriologic outcomes were assessed during a post-therapy/test of cure visit that took place between Days 17 and 24 (as shown in the generalized study design depicted in Figure 1). This visit took place after the end of therapy visit (Days 10—13) to allow early relapses to be counted as failures and thus provides a rigorous test of antibacterial efficacy.

The primary objective of the comparator-controlled studies was to demonstrate equivalence in clinical efficacy of telithromycin and comparator antibacterial treatment at the post-therapy/test of cure visit in the per-protocol population. The primary objective of the noncomparative studies was to demonstrate clinical efficacy and enrich the clinical trial database with additional information regarding pathogens of interest. Clinical outcome assessment was based on clinical signs, symptoms, and X-ray findings, and classified as cure, failure or indeterminate. Patients were classified as cured if clinical signs and symptoms were assessed as having returned to the preinfection state or shown improvement and, for CAP patients, if X-ray findings showed improvement or lack of progression. Subjects with unchanged or worsening symptoms or lack of clinical improvement requiring additional antibiotics or subsequent treatment were classified as failure. Satisfactory bacteriologic outcome was defined as documented eradication of the causative pathogen or clinical improvement to the extent that a follow-up culture could not be obtained and the pathogen was, therefore, presumed to be eradicated. Presumed bacterial failure occurred when, by definition, clinical failure was the outcome. Indeterminate clinical and bacteriologic responses were excluded from efficacy analyses.

Safety

Safety was evaluated at each visit on the basis of physical examinations, vital signs, 12-lead electrocardiograms, and standard clinical laboratory tests. Adverse events (AEs) reported by the patient or observed by the investigator were recorded throughout the study. AEs included any sign, symptom, syndrome, or illness that appeared or worsened in a patient during the period of clinical observation, and which may have impaired the well-being of the patient. These events included all laboratory findings or results of other diagnostic procedures that were considered to be clinically relevant. Clinically noteworthy abnormal laboratory values were those values considered medically important by the study sponsor according to predefined criteria. The investigator recorded the nature and severity (mild, moderate, severe) of any AE, as well as the time of onset, time course of the effects, and relation to study treatment.

Data analysis

All patients with a confirmed diagnosis of the disease indicated for therapy in each study who received at least one dose of study medication were included in the modified intent to treat (mITT) population. The bacteriologically evaluable mITT (bmITT) population included all mITT patients with a microbiologically confirmed pathogen isolated at study entry. Patients with no major protocol deviations after randomization were evaluated clinically

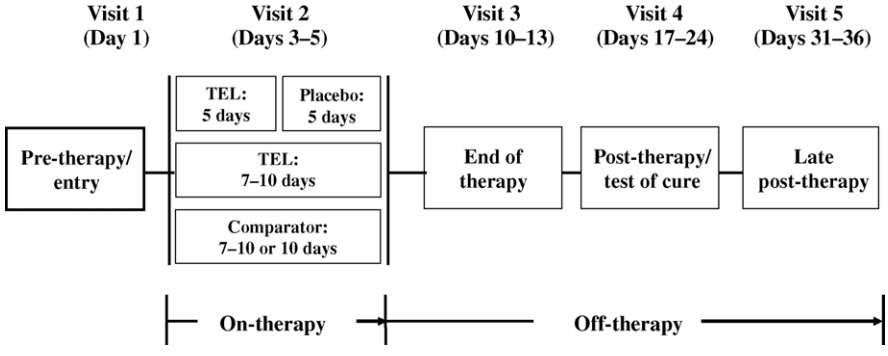

Figure 1 Generalized design for Phase III studies of telithromycin (TEL).

on a per-protocol basis (PPc population). The bacteriologic per-protocol population (PPb) included all patients in the per-protocol population who had a causative pathogen isolated at the pre-therapy visit and a classifiable bacteriologic response at the post-therapy/test of cure visit. All patients who received at least one dose of the study medication and who had at least one safety assessment after the start of treatment were included in the safety population.

Patients infected with *S. pneumoniae* were pooled from all treated indications to form a subgroup. Pooling of patients who received telithromycin for 5—10 days for acute sinusitis and 7—10 days for CAP (5 days in one CAP study) was permitted as these regimens have been shown in previous studies to be of equivalent clinical and bacteriologic efficacy.[24,25] Clinical and bacteriologic outcomes in patients with pneumococcal infection, including those with resistant strains, were determined. Standard errors of the mean were calculated for clinical cure rates.

Results

Patients

S. pneumoniae was identified as the sole pathogen or in combination with another pathogen(s) in 704 patients — 34.2% of bacteriologically evaluable patients ($n = 2060$, bmITT) and 12.7% of the total patient population ($n = 5534$, mITT). Of this subgroup with *S. pneumoniae* infections, 555 individuals received telithromycin and 149 were treated with a comparator drug (bmITT population; Table 1).

In these studies, the two treatment groups were well matched with regard to sex and ethnicity (Table 2). The majority of patients (>80%) in both groups were adults aged >18 years, although there was a slightly higher proportion of patients aged ≥65 years in the comparator group than in the telithromycin group (17.4% vs. 11.5%, respectively) (Table 2). Most patients (68—80%) in both groups had disease of moderate severity. However, the proportion of patients with mild or severe disease was slightly higher in the telithromycin group (19.1% vs. 13.4% and 13.3% vs. 6.7%, respectively) and there was a higher proportion of patients with moderate disease in the comparator group (Table 2).

Table 2 Key demographics and baseline infection characteristics across all studies for patients infected with *S. pneumoniae* as the sole pathogen or in combination with another pathogen(s) (bmITT population).

	No. of patients (%)	
	Telithromycin ($n = 555$)	Comparators ($n = 149$)
Sex		
Male	341 (61.4)	84 (56.4)
Female	214 (38.6)	65 (43.6)
Age (years)		
13—18	10 (1.8)	2 (1.3)
>18—<65	481 (86.7)	121 (81.2)
≥65	64 (11.5)	26 (17.4)
Ethnicity		
White	348 (62.7)	101 (67.8)
Black	157 (28.3)	36 (24.2)
Asian/Oriental	8 (1.4)	4 (2.7)
Other	42 (7.6)	8 (5.4)
Severity[a]		
Mild	106 (19.1)	20 (13.4)
Moderate	375 (67.6)	119 (79.9)
Severe	74 (13.3)	10 (6.7)

bmITT, bacteriologically evaluable modified intent to treat population.
[a] As assessed by the investigator.

In vitro susceptibility

Of 495 pneumococcal isolates from respiratory samples and blood cultures taken from the telithromycin-treated patients who underwent MIC evaluation (bmITT population), 493 (99.6%) were inhibited by telithromycin at an MIC of ≤1 mg/L (modal MIC 0.008 mg/L). The remaining two strains, both of which were resistant to penicillin and erythromycin, had a telithromycin MIC of 2.0 mg/L.

A total of 94 patients (bmITT population) who received telithromycin had positive blood cultures for pneumococcal disease. All of these individuals were treated for CAP, and all 83 isolates from this group for which MICs were calculated were inhibited by telithromycin at an MIC of ≤1 mg/L (modal MIC 0.008 mg/L).

Clinical and bacteriologic outcomes

The respective clinical cure rates for telithromycin and comparator agents among PPb patients infected with *S. pneumoniae* were: 94.3% (300/318) and 90.0% (63/70) [CAP]; 81.5% (22/27) and 78.9% (15/19) [AECB]; 90.1% (82/91) and 87.5% (14/16) [acute sinusitis] (Figure 2). These rates were generally comparable to the overall clinical cure rates for each indication (Figure 2). Pooled clinical cure rates for patients infected with *S. pneumoniae* (all indications) were similar after telithromycin or comparator treatment in both the PPb (92.7% [404/436] vs. 87.6% [92/105]) and the bmITT populations (91.7% [473/516] vs. 85.8% [115/134],

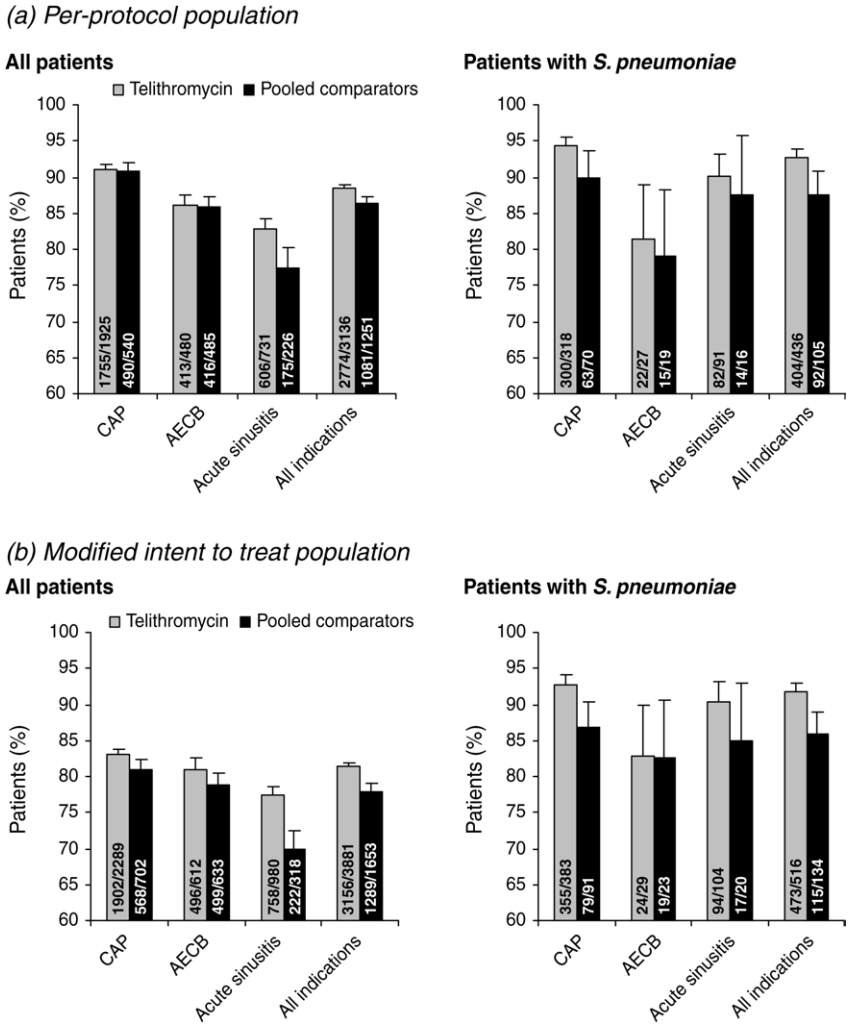

Figure 2 Clinical cure rates (improvement or return to preinfection state) in all patients and those with *S. pneumoniae* infection at the post-therapy/test of cure visit after treatment with telithromycin 800 mg once daily or a comparator antibacterial for community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB), or acute sinusitis (per-protocol [a] and modified intent to treat [b] populations).

respectively). In addition, cure rates after treatment with telithromycin vs. comparator in the overall patient populations were comparable (PPc: 88.5% [2774/3136] vs. 86.4% [1081/1251]; mITT: 81.3% [3156/3881] vs. 78.0% [1289/1653], respectively).

Good clinical cure and bacteriologic eradication rates were also reported with telithromycin in patients with infections caused by *S. pneumoniae* with reduced susceptibility to either penicillin and/or erythromycin (Table 3). Clinical cure rates in patients with isolates resistant to penicillin compared favorably with comparators, 28/34 (82.4%) and 5/7 for telithromycin and pooled comparators (PPb population). Corresponding rates of satisfactory bacteriologic outcome were 28/34 (82.4%) and 6/7, respectively. Clinical cure rates in patients with erythromycin-resistant strains were 44/52 (84.6%) and 11/14 (78.6%) with telithromycin and pooled comparators, respectively (PPb population). Similar clinical cure patterns were seen in the bmITT population. In patients with strains of *S. pneumoniae* with reduced susceptibility to both penicillin and erythromycin, clinical cure rates were 30/36 (83.3%) and 8/10, respectively (PPb population); similar rates were again observed in the bmITT population.

Of 82 patients with pneumococcal bacteremia who were evaluable on a per-protocol basis, 74 (90.2%) were clinically cured and 77 (93.9%) achieved a satisfactory bacteriologic outcome (eradication or presumed eradication) after treatment with telithromycin. The clinical cure and satisfactory bacteriologic outcome rates in the pooled comparator group for this category were both 15/19 (78.9%). Clinical cure was achieved in

Table 3 Rates of clinical cure[a] and satisfactory bacteriologic outcome[b] at post-therapy/test of cure visit after treatment with either telithromycin 800 mg daily or a comparator antibacterial for community-acquired respiratory tract infections caused by *S. pneumoniae*[c] with reduced susceptibility to either penicillin or erythromycin.

	No. of patients (%)			
	Telithromycin		Pooled comparators	
	Clinical cure	Satisfactory bacteriologic outcome	Clinical cure	Satisfactory bacteriologic outcome
PPb population				
PEN-S	293/315 (93.0)	299/315 (94.9)	71/80 (88.8)	70/80 (87.5)
PEN-I	40/41 (97.6)	41/41 (100)	7/8	7/8
PEN-R	28/34 (82.4)	28/34 (82.4)	5/7	6/7
ERY-S	317/338 (93.8)	324/338 (95.9)	72/81 (88.9)	71/81 (87.7)
ERY-R	44/52 (84.6)	44/52 (84.6)	11/14 (78.6)	12/14 (85.7)
PEN-I/PEN-R + ERY-R	30/36 (83.3)	30/36 (83.3)	8/10	9/10
bmITT population				
PEN-S	339/368 (92.1)	345/363 (95.0)	87/100 (87.0)	87/99 (87.9)
PEN-I	46/48 (95.8)	48/49 (98.0)	10/11 (90.9)	10/12 (83.3)
PEN-R	34/42 (81.0)	35/42 (83.3)	6/9	7/9
ERY-S	369/399 (92.5)	378/395 (95.7)	91/105 (86.7)	91/105 (86.7)
ERY-R	51/60 (85.0)	51/60 (85.0)	12/15 (80.0)	13/15 (86.7)
PEN-I/PEN-R + ERY-R	37/44 (84.1)	37/44 (84.1)	9/11 (81.8)	10/11 (90.9)

bmITT, bacteriologically evaluable modified intent to treat population; ERY-R, resistant to erythromycin (MIC $\geq$1.0 mg/L); ERY-S, susceptible to erythromycin (MIC $\leq$0.25 mg/L); PEN-I, intermediate susceptibility to penicillin (MIC 0.12—1.0 mg/L); PEN-I/PEN-R, not susceptible to penicillin (includes penicillin-intermediate and -resistant isolates); PEN-R, resistant to penicillin (MIC $\geq$2.0 mg/L); PEN-S, susceptible to penicillin (MIC $\leq$0.06 mg/L); PPb, bacteriologically evaluable per-protocol population.

[a] Clinical improvement or return to preinfection state.

[b] Documented or presumed eradication.

[c] As the sole pathogen or as part of a mixed infection.

5/7 telithromycin-treated bacteremic patients infected with penicillin-resistant isolates, and 8/10 patients with isolates resistant to erythromycin, representing two clinical failures: *S. pneumoniae* isolated from these two patients were resistant to both penicillin and erythromycin.

Safety

As shown in Figure 3, telithromycin had a safety and tolerability profile for the five most common AEs which was similar to those of comparators across the pooled studies. Treatment-emergent AEs were reported by 1746/4045 (43.2%) telithromycin recipients and 835/1715 (48.7%) patients who received comparator antibacterials. Treatment-emergent AEs considered by investigators to be possibly related to study medication were seen in 1071/4045 (26.5%) and 505/1715 (29.4%) patients in the two treatment groups, respectively. The most frequently reported treatment-related AEs were diarrhea (telithromycin 7.6%; comparators 8.9%), nausea (telithromycin 5.3%; comparators 4.4%), and headache (telithromycin 1.5%; comparators 2.4%). Other treatment-related AEs included abnormal liver function tests (telithromycin 1.8% [71/4045]; comparators 1.7% [29/1715]) and visual disturbances, which occurred in 0.4% (15/4045) of telithromycin patients and 0.2% (3/1715) of comparator patients. In both groups, the AEs were of mild to moderate intensity in the majority of cases reported. Few patients in either treatment group discontinued due to AEs (telithromycin 2.3%; comparators 3.0%), and there were no treatment-related deaths. There were few clinically noteworthy abnormal laboratory values (167/4045 telithromycin-treated patients [4.0%] and 75/1715 comparator-treated patients [4.4%]), which included assessment of cardiac (including QT interval), liver, and renal function.

Discussion

This pooled analysis focused on the clinical and bacteriologic efficacy of the new ketolide, telithromycin, in 555 patients with predominantly mild to moderate community-acquired pneumococcal RTIs including CAP, AECB, and ABS. Overall, results from the 14 trials confirm that this antibacterial, at a dosage of 800 mg once daily, achieves high rates of clinical cure and satisfactory bacteriologic outcome in patients infected with *S. pneumoniae*, with effi-

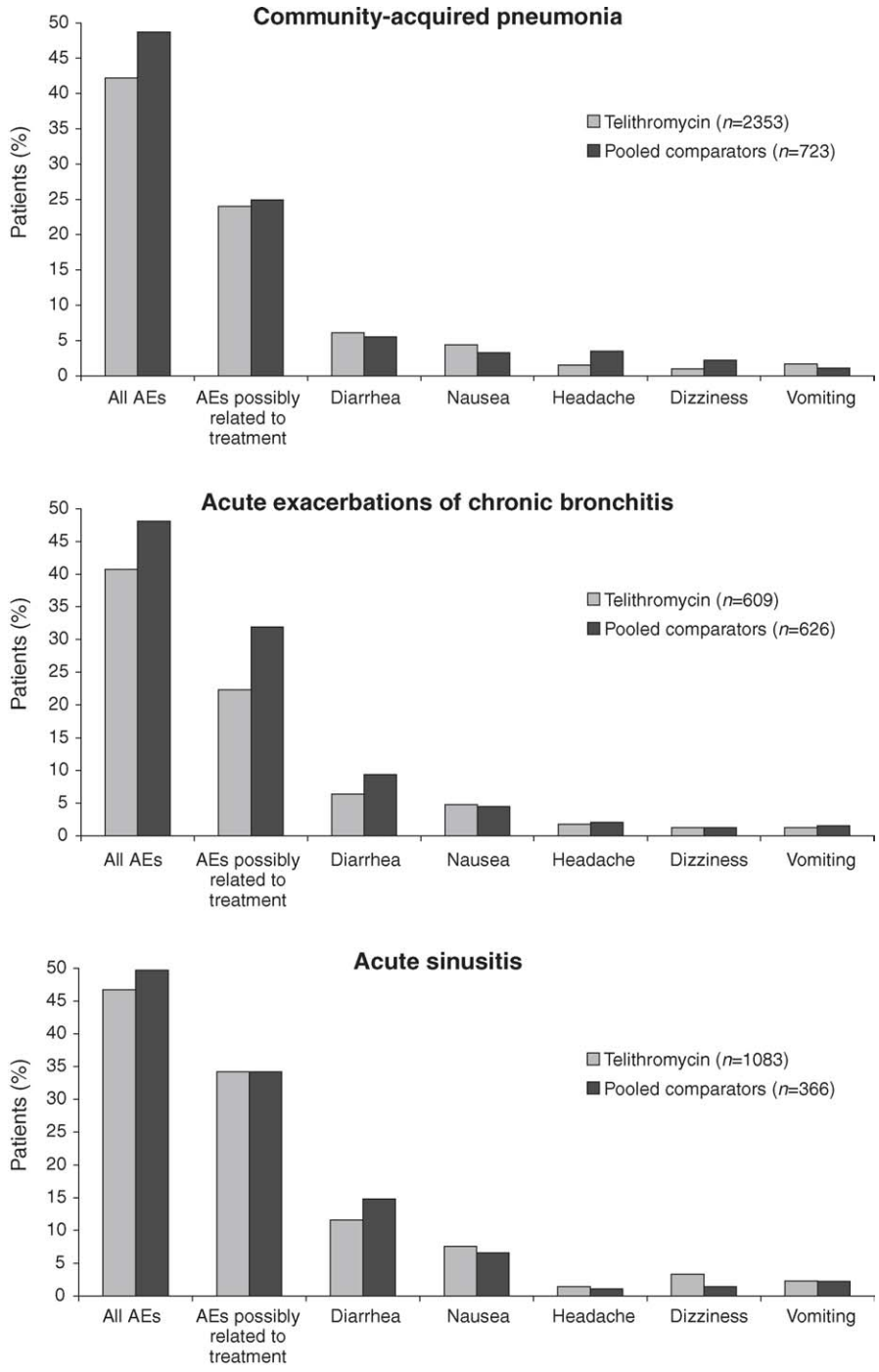

Figure 3 Frequencies of treatment-emergent adverse events (AEs) for telithromycin and comparator antibacterials by indication. All events reported are presented, together with those considered by investigators to be possibly related to study treatment and the five most common individual AEs possibly related to treatment.

cacy equivalent to that seen with a range of standard first-line antibacterial agents.[6,38–43] For all indications combined, telithromycin achieved a clinical cure rate of 93% in patients with pneumococcal infections (PPb population); the corresponding cure rate for comparator agents was 88%. Similar results were seen in the more conservative analysis of the bmITT population that includes protocol violators and incomplete data. For each of the RTI indications analyzed, the overall clinical cure rates associated with telithromycin treatment (81.5% [AECB]; 90.1% [acute sinusitis]; 94.3% [CAP]) were higher than those seen with comparators (78.9% [AECB]; 87.5% [acute sinusitis]; 90.0% [CAP]) in the respective per-protocol patient populations. Furthermore, clinical cure and bacteriologic eradi-

cation (eradication/presumed eradication) rates in telithromycin patients with documented *S. pneumoniae* infection were similar to those reported for the total patient population covered by the analysis. The efficacy of telithromycin against *S. pneumoniae* also extended to patients infected with strains with reduced susceptibility to penicillin (12.8% of isolates) and/or erythromycin (9.4% of isolates). Although these results are based on low numbers of isolates, they complement those from previous analyses, demonstrating that telithromycin provides clinical and bacteriologic efficacy in infections caused by common and atypical RTI pathogens, including those caused by resistant pathogens.[44–47] The current analysis is limited by the fact that data were pooled from 14 studies, each of which had focused on one indication and treatment regimen. The potential effects of variable treatment regimens on clinical outcome were not addressed in this study. Furthermore, any differences in efficacy between telithromycin and individual comparators would not be evident in the current analysis, as the data for comparator agents were pooled.

As *S. pneumoniae* represents the leading bacterial cause of community-acquired RTIs and is associated with a high complication rate compared to other pathogens, physicians prescribing empiric therapy for such infections need to recognize the importance of choosing an agent that can effectively target this organism as well as other common typical and atypical respiratory pathogens. At present, β-lactams and macrolides are the most commonly used drugs for the first-line management of community-acquired RTIs. However, the clinical usefulness of these agents may be threatened by the high and increasing prevalence of antibiotic resistance, particularly among isolates of *S. pneumoniae*.[15] Antibacterial susceptibility surveillance programs have indicated significant levels of resistance to penicillin and erythromycin among respiratory tract isolates of *S. pneumoniae*, with global resistance rates of 22.1% (penicillin) and 31.1% (erythromycin) reported in one study of respiratory isolates collected between 1999 and 2000.[14] The quinolones are an attractive option for use against resistant *S. pneumoniae*; however, as with other antibiotics, occurrence of resistance is correlated with their widespread use. Because of their broad spectrum, some experts may recommend use of an alternative antibiotic for first-line use in the community setting.

Emerging data from retrospective analyses and case reports indicate that increasing pneumococcal resistance may be compromising the efficacy of current therapies in patients with community-acquired RTIs to a greater extent than has been suggested by the results of clinical trials.[48] In recent years, there have been several reports of bacteremia, breakthrough sepsis,[49–52] or fatal outcome[53–55] associated with resistant pneumococcal strains in patients with lower RTIs who were treated with macrolides as first-line therapy. Other reports detail macrolide treatment failure in CAP patients who were subsequently treated successfully with other antibacterial agents.[56,57] Such treatment failures may be explained, in part, by an inability of some macrolides to achieve sufficiently high tissue concentrations at currently recommended dosages to be effective against these pathogens, in an environment with increasingly higher erythromycin MICs.[58] These observations of treatment failures suggest that there is a need for new antibacterials, such as telithromycin, which retain efficacy against antibiotic-resistant *S. pneumoniae* infections.

Telithromycin has a spectrum of activity allowing first-line use against community-acquired RTIs, providing coverage of common and atypical bacterial pathogens. Although structurally related to the macrolides, it has a distinct microbiologic profile — due to differences in its chemical structure — that confers activity against resistant pneumococcal strains. The most notable structural modification is the replacement of the L-cladinose group with a keto group at position C3 of the macrolactone ring that enables telithromycin to bind to its target without the associated inducible macrolide–lincosamide–streptogramin$_B$ (MLS_B) resistance that many respiratory pathogens now exhibit.[59] In addition, a carbamate extension at positions C11 and 12 allows telithromycin to bind to wild-type ribosomes with an affinity 10 times greater than that of erythromycin and 6 times that of clarithromycin, and its affinity for MLS_B-resistant ribosomes is over 20 times greater than that of either macrolide.[59] Once-daily administration of telithromycin 800 mg is sufficient to achieve drug concentrations in respiratory tissues that exceed MICs for key pathogens such as *S. pneumoniae* — including resistant strains — for up to 24 hours after each dose.[60,61]

Patients with CAP caused by *S. pneumoniae* are at risk of progression to bacteremia and septic complications, such as respiratory failure, meningitis, pleural effusions, and empyema, which may be fatal.[54,62,63] With the outpatient treatment of mild to moderate CAP, many patients are treated without cultures being available. Although there is little clinical evidence to indicate that current first-line therapies should no longer be used to treat pneumococcal RTIs, the rising incidence of resistance among *S. pneumoniae*, and its association with bacteremia, suggest that new options for first-line therapy effective against resistant pneumococci

may soon be needed. In the present analysis, telithromycin showed high rates of clinical and bacteriologic efficacy (>90%) in patients with pneumococcal bacteremia, who represented more than 10% of those with a pneumococcal etiology. This efficacy extended to those bacteremic patients with penicillin- or erythromycin-resistant strains.

With regard to safety, telithromycin was well tolerated in patients with CAP, AECB, and acute sinusitis. The nature and frequency of AEs were similar in the telithromycin and pooled comparator groups. Most AEs were of mild to moderate severity and very few patients withdrew because of AEs.

In conclusion, telithromycin 800 mg once daily shows favorable clinical and bacteriologic efficacy as well as good tolerability in the treatment of community-acquired RTIs caused by *S. pneumoniae* and other common respiratory tract pathogens. This efficacy extends to patients with pneumococcal bacteremia and to pneumococcal strains with reduced susceptibility to penicillin and/or erythromycin. Given that *S. pneumoniae* remains the major bacterial cause of community-acquired RTIs, and that penicillin and macrolide resistance are increasing among this species, the findings of this pooled analysis support the use of telithromycin as a first-line empiric treatment in this setting.

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